

Chronic Heartburn: Causes and Remedies

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At the junction of esophagus and stomach there exists a smooth muscle sphincteric mechanism which forms the functional pressure barrier normally preventing reflux of highly acid gastric material into the esophagus. This gastroesophageal sphincter is illustrated schematically in Figure 1. Clinical research on the mechanisms controlling the action of this sphincter and its incompetence in patients with gastroesophageal reflux has been in progress for the past three years at the Naval Hospital Philadelphia under the support of Bureau of Medicine and Surgery. These studies were initially undertaken because of the high incidence of symptomatic reflux in military personnel, and the frequent resulting loss of time from duty secondary to this problem.

The gastrointestinal hormone gastrin has been well established as a primary factor in stimulating acid secretion by the stomach. Gastrin has also been identified as important in the control of pressure in the gastroesophageal sphincter. Teleologically, it seems quite reasonable that this hormone secreted by the stomach should regulate sphincter closure and thereby maintain an effective barrier against acid reflex in the esophagus (1). Increase in sphincter pressure should occur concomitantly with gastrin stimulation of acid output (Figure 1).

These studies were quickly followed by the observation that this sphincteric mechanism could be strengthened by the administration of alkalinizing agents of various kinds into the stomach (2). Thus, not only sodium bicarbonate and sodium hydroxide but also commercial antacid agents, the mainstay of therapy for patients with gastroesophageal reflux, were shown to increase pressure in this sphincteric barrier. The studies were initially performed in normal volunteers, but subsequently pursued in a group of patients with symptomatic incompetence of this sphincter having the clinical hallmark of this abnormality, chronic heartburn. In the latter, the administration of usual clinical doses of antacids produced considerable increases in the sphincter pressure, so that the effective pressure was elevated from a low or incompetent level to a level similar to that found in the resting normal subject. These results indicated that

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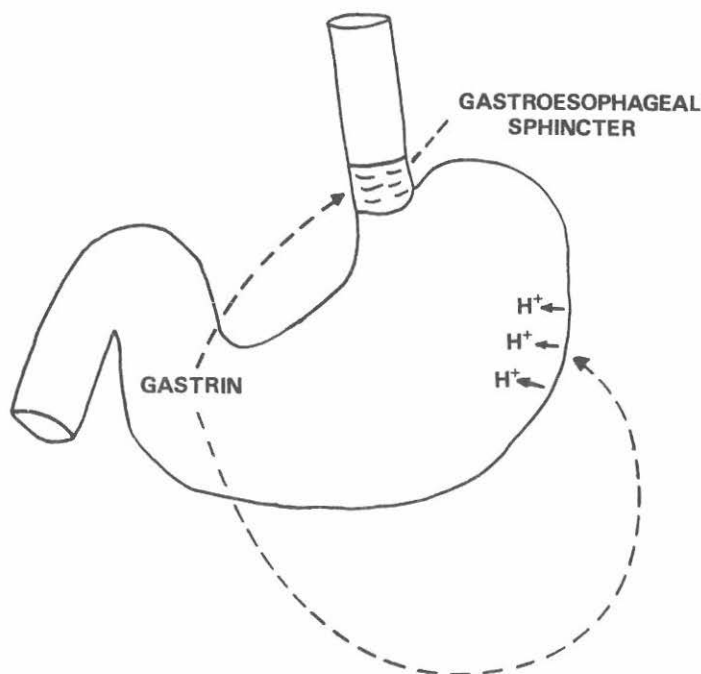


Figure 1 — Schematic representation of the relationship of the hormone gastrin to hydrogen ion concentration and gastroesophageal sphincter pressure.

the therapy of the heartburn patient with frequent alkalinization had a dual rationale, not only the neutralization of the acid gastric contents but also the strengthening of the gastroesophageal sphincter pressure barrier.

Because of the common problem of heartburn being produced by certain specific foods, smoking, and possibly also by coffee ingestion, a series of investigations was undertaken to clarify the mechanism for these observations. LCDR Otto T. Nevel, MC USN working in the Gastrointestinal Laboratory at the Naval Hospital Philadelphia has completed an extensive study of the effect of food on the gastroesophageal sphincter mechanism (3). The results of these studies indicate that a relatively high protein meal produces an increase in the sphincter pressure. This effect is not surprising and is consistent with the initial studies on the effect of the hormone gastrin on this sphincter, since protein has long been known to be an effective stimulator of endogenous gastrin release. A pure carbohydrate meal was shown to produce a slight increase in the pressure in the sphincter. The effect of the ingestion of a pure fat meal was most dramatic. Almost immediate marked decreases in pressure in the gastroesophageal sphincter were produced after the ingestion of a fat meal or after administration of the same meal directly into the duodenum. The decreases in pressure were so marked

that normal subjects noted the appearance of symptoms of gastric reflux (heartburn) during the course of these studies. In addition, the effect of fat ingestion was shown to persist for at least one hour after the ingestion of this meal.

A more physiologic form of a meal would include a combination of foods rather than pure protein or fat. Therefore, Dr. Nebel subsequently studied the effect of combining the protein and fat meals into a single meal (4). The ingestion of the combined protein/fat meal by normal subjects resulted in slight decreases in sphincter pressure. In other words, it appeared that the fat combined with protein had the effect of abolishing the normal protective action of protein in increasing pressure in the gastroesophageal sphincter. It was concluded, that calorie for calorie, fat had a more definite effect on this sphincter than did protein.

As stated previously the mainstay in the therapy of gastroesophageal reflux has been gastric alkalization, with the express purpose of neutralizing the acid gastric material. Our initial studies had indicated that simple alkalization of the stomach did also increase the sphincter pressure, apparently through the release of endogenous gastrin from the antrum of the stomach. Therefore, the effect of antacid therapy on the inhibitory action of fat on the gastroesophageal sphincter seemed of clinical importance. These effects were investigated in other normal subjects by giving the fat meal as used in the previous studies followed by the usual therapeutic dose of antacid medication at a time when the inhibitory effect of fat was well established. These studies indicated that, although, the fat consistently produced marked decreases in sphincter pressure, the subsequent ingestion of antacid produced a rise in pressure up to the previous resting levels (4). Thus, the gastrin releasing effect of alkalization blocked the fat inhibition of sphincter pressure. In more detailed studies, Dr. Nebel has shown that the mechanism for this effect is through the competitive interaction of the gastrointestinal hormones gastrin and cholecystokinin (5). Of more importance to the clinician is the fact that antacid therapy should have a very positive action in the postprandial symptoms of gastroesophageal reflux, at least those produced by fat ingestion.

Since many patients with symptomatic reflux complain of increased symptoms when smoking and possibly when ingesting coffee, we have pursued clinical investigations into the effects of these agents on the gastroesophageal sphincter. Lt George W. Dennish, MC USN working in the Gastrointestinal Laboratory has shown that cigarette smoking has a very rapid deleterious effect on sphincter pressure in normal subjects (6). This effect was shown to produce decreases in pressure into a range seen in patients with chronic heartburn within three to four minutes after the initiation of smoking. The effect, however, was quite transient, and sphincter pressures returned to normal within five minutes

of terminating smoking. Further studies by Dr. Dennish on the effect of caffeine and coffee ingestion indicated less striking, but slight, decreases in sphincter pressure produced by caffeine (7). The clinical importance of this latter observation would appear to be that, although, the sphincter pressure does not decrease markedly, caffeine does have a well established action on the gastric parietal cell to increase gastric acid secretion. This effect, combined with the slight lowering of sphincter pressure, may well explain why patients with an already incompetent gastroesophageal sphincter note increased symptomatology after coffee ingestion. In fact, the common habit of having a coffee and cigarette after a meal seems to be particularly disadvantageous to the heartburn sufferer.

Further studies on the effect of foods have revealed an intriguing inhibition of gastroesophageal sphincter pressure produced by chocolate ingestion. We have long observed chocolate to be one of the factors producing symptoms in many of our patients, and during the past year these effects have been studied by LCDR John C. Babka, MC USN. The results of Dr. Babka's investigations indicate that, similar to fat ingestion, there are very striking decreases in sphincter pressure within the first few minutes after chocolate ingestion, and that this effect persists for at least a full hour (8). Although we initially believed the effect to be due to the fat content of the chocolate, it would appear that this is not the case since defatted chocolate syrup produces the same marked decreases in sphincter pressure. The mechanism for this action is less clear, but is believed to result from the ability of the caffeine and theobromine in chocolate to stimulate internal hormone actions, probably

TABLE 1
Factors Known to Effect Gastroesophageal Sphincter Pressure

<u>Increased Pressure</u>		<u>Decrease Pressure</u>	
<u>Agent</u>	<u>Mechanism</u>	<u>Agent</u>	<u>Mechanism</u>
Gastrin/Pentagastrin	Direct Effect	Secretin	Blocks Gastrin
Alkali	{ Gastrin Release	Acid	Gastrin Inhibition and Secretin Release
Protein		Fat	Probably Cholecystokinin Release
Carbohydrate		Smoking	Probably Nicotine Effect
Bethanechol	Direct Effect and Gastrin Release	Caffeine (coffee)	{ Probably Cyclic AMP Production
Edrophonium	Acetylcholine Production	Chocolate	

working through the production of increased tissue cyclic 3' 5' adenosine monophosphate (cyclic AMP). Further studies on the interrelationship of gastrin, gastric alkalization, and chocolate ingestion are in progress.

Having detailed much of the mechanisms by which the gastroesophageal sphincter tends to lose its effective pressure, and thus contribute to the reflux of gastric material into the esophagus, we next turned our attention to other mechanisms for promoting increases in sphincter pressure. LCDR Raymond L. Farrell, MC USN and CDR Gerald T. Roling, MC USN have shown that marked increases in sphincter pressure occur in normal subjects following parenteral injection of parasympathomimetic agents, particularly bethanecol (9). In this study, following the injection of 5 mg of bethanecol gastroesophageal sphincter pressures in normal subjects rose from a mean value of 15.0 mm Hg to a peak of 31.5 mm Hg within thirty-five minutes after injection. The pressure remained elevated for at least one hour following the injection. Further studies on the mechanisms of this action would appear to indicate that the cholinergic stimulation is in some way interrelated with endogenous gastrin release. Since various maneuvers to inhibit gastrin were shown to decrease the effectiveness of bethanecol in raising sphincter pressure (9).

More recent studies with various means of stimulating an increased pressure in the gastroesophageal sphincter have been applied to patients with clinical incompetence of this smooth muscle pressure barrier. Doctors Farrell and Roling have shown that patients with low resting sphincter pressures and chronic symptomatic reflux, that is chronic heartburn, will respond to various stimuli by increasing their effective pressure to a level consistent with that found in normal subjects (10). This effect has been produced by injection of the hormone gastrin or by the administration of alkali into the stomach producing endogenous gastrin release. In addition, Dr. Farrell has recently shown that protein ingestion in patients with reflux symptoms will result in considerable increases in sphincter pressure (11).

Of even greater importance is the effect of the cholinergic agent bethanecol on sphincter pressure in these patients. Initial studies with bethanecol injection indicated that resting pressures could be increased from a low level of approximately 5 mm Hg to a peak of almost 20 mm Hg within thirty minutes following the injection. This potentially useful therapeutic effect was further evaluated using an oral form of this same drug. In the same subjects 25 mg of bethanecol orally produced changes in sphincter pressure from an incompetent level of 7 mm Hg to a peak level of 6.4 mm Hg within forty-five minutes after ingestion. More importantly, the pressure was maintained above the expected lower limit of normal (10 mm Hg) for a full two hour period after ingestion of the drug. These results indicate that the patient having an incompetent

gastroesophageal sphincter might receive therapeutic benefit from attempts to elevate the pressure. In fact, the remarkable ability of these various stimulating agents to increase the pressure in these subjects from abnormal to a "normal" level strengthens the hypothesis of a possible therapeutic use for such drugs.

The goal of any clinical investigator should be to develop his observations on basic physiology in the laboratory to the point where they have potential application to diagnostics or therapeutics at the bedside. To this end our studies on the use of various stimulators of gastroesophageal sphincter pressure have lead to the realization that cholinergic stimulation may result in an effective long-lasting medical treatment for chronic gastroesophageal reflux. At the present time this hypothesis is being tested at the Naval Hospital, Philadelphia through the mechanism of a double blinded controlled trial supervised by Dr. Farrell on patients with chronic reflux who are referred to the Gastrointestinal Unit of this hospital for evaluation and management.

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